Evaluation of toe pressure and transcutaneous oxygen measurements in management of chronic critical leg ischemia: A diagnostic randomized clinical trial

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Objective: **The definition of critical limb ischemia (CLI) requiring vascular intervention is still under debate. The clinical eye of the physician and ankle blood pressure measurements used so far may fall short in appreciation of the severity of disease, which makes decision-making for a vascular intervention subjective. In previous studies two simple functional tests, ie, transcutaneous oxygen pressure ($tcPO_2$) and toe blood pressure (TP) measurements, provided reliable information about the need for vascular intervention. Therefore we evaluated the diagnostic value of $tcPO_2$ and TP in management of clinically suspected critical leg ischemia.**

Study design: **This was a diagnostic randomized controlled clinical trial. Subjects were ambulatory and hospitalized patients in a referral university hospital.**

Methods: **Ninety-six patients (128 legs) with clinically suspected critical limb ischemia were referred to the vascular laboratory for routine investigation. Two diagnostic management strategies were compared: conventional strategy, ie, clinical judgment and ankle pressure determined the diagnostic and therapeutic approach, and a new strategy in which $tcPO_2$ and TP determined the diagnostic and therapeutic approach. Main outcome measures included clinical outcome, defined as pain relief, wound healing, and limb survival.**

Results: **At 18-month follow-up, 26 of 62 legs treated with the conventional approach and 28 of 66 legs treated with the new approach were treated conservatively. The new method did not score significantly different from the conventional method insofar as clinical outcome: pain score, 50 versus 48; number of amputations, 8 versus 10; and number of deaths, 11 versus 8 deaths, respectively.**

Conclusion: **Two simple objective diagnostic tests, TP and $tcPO_2$, did not improve clinical outcome when incorporated into routine management of suspected critical limb ischemia. Nevertheless, these techniques might still be helpful for physicians less experienced with treating critical limb ischemia and who are in doubt regarding the need for vascular intervention. (J Vasc Surg 2003;38:528-34.)**

The definition of critical leg ischemia (CLI) that requires intervention is still under debate.[1-7] According to the TransAtlantic Inter-Society Consensus on Management of Peripheral Arterial Disease the term CLI can be used for all limbs with chronic ischemic rest pain, ulcer, or gangrene, attributable to objectively proved arterial occlusive disease.[3] However, these clinical characteristics are not specific for CLI, but can also be caused by other diseases. Particularly in patients with multifactorial disease, eg, peripheral vascular disease in combination with diabetes or venous insufficiency, the indication for intervention in suspected CLI can be difficult. Various consensus documents have proposed criteria based on ankle blood pressure (AP). However, objective criteria have never achieved full consensus.[5-7] The latest consensus does not define objective criteria for vascular intervention in clinically suspected CLI. At present, diagnostic angiography or duplex scanning is frequently performed to evaluate the extent of vascular obstruction. The limitation of these investigations is that they do not provide functional information about tissue perfusion, but only anatomic information, which is not always related to the severity of clinical symptoms and clinical outcome of the disease.

Therefore the indication for vascular intervention is frequently based on the skilled view of a vascular specialist. The timing for vascular intervention is difficult, because vascular intervention is accompanied by serious side effects, eg, risk of operation, wound infection, and early occlusion, ultimately resulting in amputation or death.[8] In contrast, postponing intervention can harm the patient. Moreover, CLI has a considerable effect on health-related quality of

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Supported by grant 96-113 from The Netherlands Heart Foundation.
Competition of interest: none.
Presented as a poster at the Twenty-second Annual Meeting of the European Society for Microcirculation, Exeter, Devon, England, Aug 28-30, 2002.

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0741-5214/2003/$30.00 + 0
doi:10.1016/S0741-5214(03)00414-2

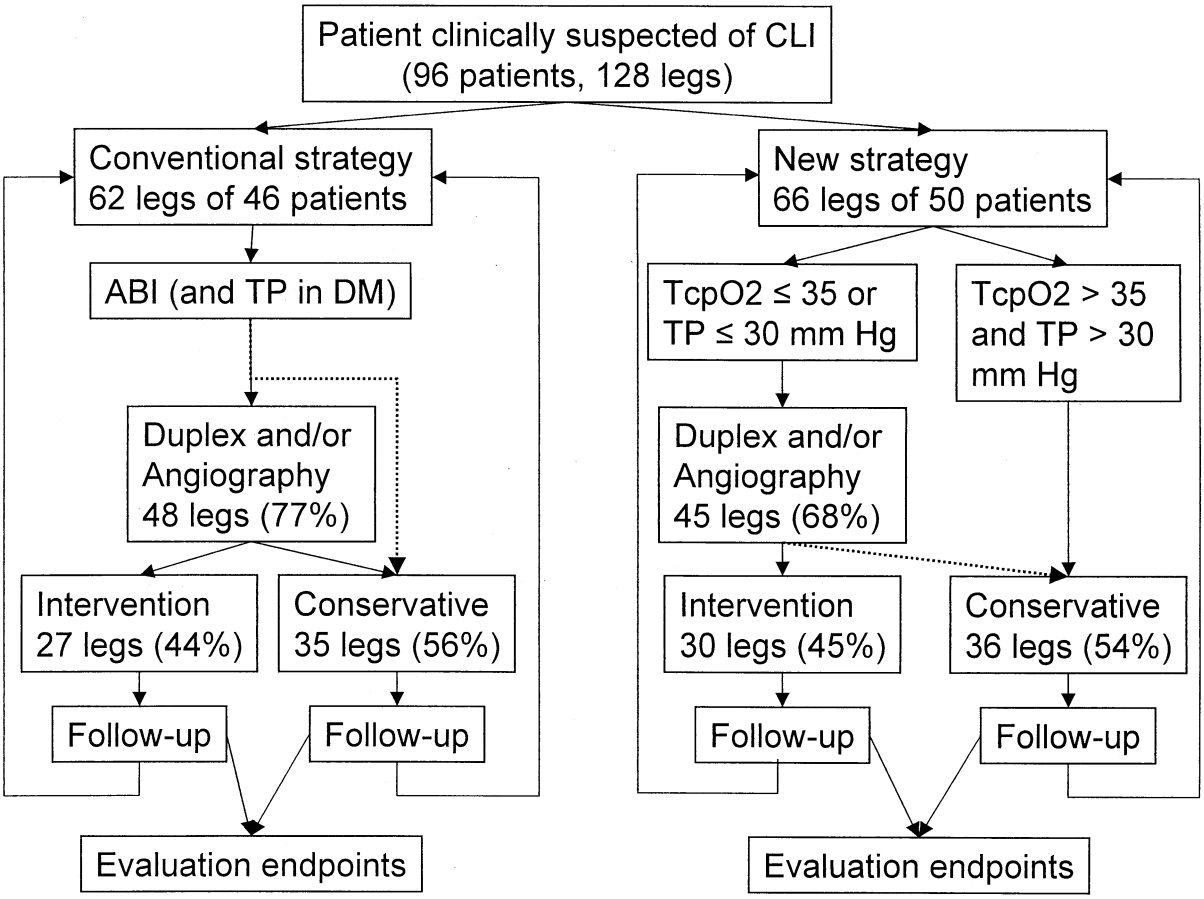

Fig 1. Scheme of randomization and follow-up.

life.[9] This leads to considerable variation between diagnostic procedures and indications for vascular intervention between hospitals and countries.[10,11]

Hence there is need for simple objective criteria to identify CLI that requires vascular intervention. Previous investigations have shown retrospectively that a combination of toe blood pressure (TP) and transcutaneous oxygen pressure ($tcPO_2$) measurements might be good indicators of CLI and subsequent need for vascular intervention.[12,13] Both are simple, quick tests that provide functional information about peripheral tissue perfusion. In actuality, it is disturbance in the peripheral (micro)circulation that causes signs and symptoms of CLI.[7,14-16] Several studies have demonstrated the diagnostic advantage of transcutaneous oxygen measurements in evaluation of arterial insufficiency of the leg.[17-20] $tcPO_2$ measurements may be used to direct therapy, because they accurately predict the presence of significant vascular disease.[17] Moreover, additional measurement of TP and $tcPO_2$ substantially increases pretest probability for vascular intervention.[7]

In the present diagnostic randomized clinical trial we compared outcome in patients with clinically suspected CLI managed with a new strategy, based on the combination of TP and $tcPO_2$ measurements and on indication duplex scans or angiograms, with that for CLI managed with the conventional strategy, based on AP measurements and duplex scans or angiograms.

PATIENTS AND METHODS

Patients. Inpatients and outpatients of the Academic Medical Center seen from April 1, 1997, to June 1, 1999, referred to the vascular laboratory for diagnostic work-up by a vascular surgeon because of clinically suspected CLI, were asked to participate in this diagnostic randomized clinical trial. Clinical CLI was defined as pain at rest in the lower leg for more than 2 weeks, ulcers that persisted for more than 2 weeks, or diffuse gangrene of the forefoot. Patients with suspected acute arterial occlusion were excluded. To improve the significance of this study we excluded the so-called clear-cut cases, leaving only patients with an uncertain diagnosis, because only in these patients was additional diagnostic effort relevant.[21] Clear-cut cases were defined as obviously severe disease, ie, presence of extensive necrosis, or clearly mild disease, ie, presence of clinical CLI but with palpable peripheral pulses.

Table I. Baseline clinical characteristics of patients

	Management strategy			
	Conventional (n = 46)		*New (n = 50)*	
	n	*%*	*n*	*%*
Demographic				
Age (y)	71 ± 12		72 ± 13	
Male/female	29/17		29/21	
Comorbidity				
Diabetes mellitus	21	46	22	46
Hypertension	20	44	22	44
History of cerebrovascular accident or transient ischemic attack	11	24	12	24
History of coronary heart disease	18	39	24	48
Vascular				
Smoking	21	46	29	58
Two legs included	15	32	17	34
Pain and quality of life				
SF-36 physical summary score	28 ± 9		29 ± 9	
SF-36 mental summary score	41 ± 12		41 ± 12	
SF-36 pain score	26 ± 10		28 ± 14	

Table II. Baseline characteristics of ischemic legs at inclusion

	Management strategy			
	Conventional (n = 62)		*New (n = 66)*	
	n	*%*	*n*	*%*
Rest pain	54	87	57	86
Ulcerations or gangrene	31	50	35	53
Previous minor amputation	4	7	4	6
Previous bypass operation	11	18	5	8
Previous PTA or TEA procedure	11	18	10	15
Ankle systolic pressure (mm Hg)	108 ± 53		91 ± 53	
Ankle-brachial pressure index	0.56 ± 0.24		0.58 ± 0.29	
Toe pressure (mm Hg)	62 ± 57*		45 ± 42	
$TcPo_2$ (mm Hg)	—		33 ± 19	
Pain and severity of clinical symptoms				
Visual analog scale of pain in involved leg	42 ± 33		41 ± 30	
Wound surface area (cm^2)†	1.7	0.5-6.0	2.4	0.5-10.9
Knighton wound severity score†	23	19-31	27	17-42

PTA, Percutaneous transluminal angioplasty; *TEA,* thromboendarterectomy.
*Toe pressure measured in 15 legs with incompressible arteries.
†Median with interquartile ranges (25%-75%).

Patients were randomized to receive either conventional treatment or the new management technique (Fig 1), which could also have consequences for the therapy assigned. The potential types of therapy were equivalent for both groups (vascular intervention or conservative therapy), but the groups differed in diagnostic information available at the time the decision was made. This differing information could lead to a different treatment and might influence clinical outcome in the end.

The randomization was performed by computer and was prestratified for the presence of diabetes mellitus and bilateral symptoms of CLI. If CLI was clinically suspected in both of a patient's legs, both legs were included in the trial, but randomization was only assigned once.

Methods. AP was measured in all patients. TP and $tcPo_2$ were measured only in patients assigned to the new strategy group. In the conventional strategy group TP was also measured in patients with diabetes mellitus and patients in whom AP was not reliable because of incompressible arteries (ankle-brachial index > 115%), because withholding any functional information about severity of disease would be unethical and unacceptable to the vascular surgeons in our department. AP, TP (PV lab, Stöpler; Electric Diagnostic Instruments, Burbank, Calif) and $tcPo_2$ (TCM3; Radiometer, Copenhagen, Denmark) at electrode temperature of 44°C were measured according to standard procedures.[14] The reproducibility of all techniques has been studied and appears to be acceptable for all techniques across the entire range of pressure.[14]

During follow-up of 18 months the diagnostic regimen was based on assigned randomization, which might have consequences for the assigned therapy and clinical outcome. Appropriate measurements, ie, AP, TP, and $tcPo_2$ and assessment of outcome parameters, were assessed at regular intervals, ie, 1, 3, 6, 9, 12, and 18 months after inclusion in the trial. The diagnostic and decision algorithm for the patients is shown in Fig 1.

According to the conventional strategy, the decision for further diagnostic imaging of the arteries, ie, primary duplex scanning, was left to the discretion of the vascular surgeon, based on clinical symptoms, findings at physical examination, and AP, as well as TP in patients with incompressible arteries. No specific levels were advocated. Angiography, ie, intra-arterial digital subtraction angiography, was performed only in patients with multilevel disease or when it was not possible to evaluate the arteries because of calcifications. The proposed therapy, whether conservative treatment, bypass grafting, or percutaneous transluminal angioplasty, was discussed at a weekly multidisciplinary meeting of vascular surgeons, intervention radiologists, and vascular technologists. The decision was made on the basis of consensus, and no specific AP or TP levels prompted conservative treatment, arterial bypass grafting, or balloon angioplasty.

According to the new strategy, the results of the combination of TP and $tcPo_2$ measurements indicated the intention for vascular intervention. This intervention, and therefore preintervention duplex scanning or angiography,

Table III. Number of amputations and interventions

	Management strategy				
	Conventional (n = 62)		*New (n = 66)*		
	n	*%*	*n*	*%*	P
Minor amputation*	6	10	9	14	.59
Major amputation	3	5	4	6	.68
Number of patients who underwent duplex scanning or angiography	48	77	45	68	.24
Total duplex scans†	50		56		
Total angiograms†	31		36		
Number of patients with vascular interventions	27	44	30	45	.83
Percutaneous transluminal angioplasty†	16		24		
Bypass surgery†	18		18		

*Minor amputations performed in patients who underwent major amputations not included.
†Multiple diagnostic procedures and interventions may be performed in one patient.

was indicated only if one of the two measurements was below the cutoff level (TP ≤ 30 mm Hg; $tcPo_2$ ≤ 35 mm Hg) and symptoms of CLI were present. The final planning of the vascular intervention, ie, indication and type, was made at the vascular consensus meeting, with the intention to perform every possible and clinical useful vascular intervention to restore TP and $tcPo_2$ measurements to above the cutoff value.

Conservative treatment in both groups included control of pain; wound and foot care including appropriate dressing, debridement, and topical antibiotic therapy; and systemic antibiotic or anticoagulant therapy, if necessary. On indication, diagnostic assessment for differential diagnosis was performed to rule out conditions such as diabetic neuropathic ulcers, venous insufficiency, and nerve compression, and appropriate treatment was administered.

Outcome parameters. The primary end point was change in the clinical situation as noted by pain relief and wound healing. Pain severity was appreciated for each leg with a visual analog scale: the patient rates leg pain by placing a mark on a line 100 mm long, with zero being equivalent to no pain and 100 being equivalent to maximum pain. Next the pain was investigated in each patient over the last month with the summary score of the pain scale of the SF-36. This is calculated from two questions in the questionnaire, and ranges from 0, representing maximum pain, to 100, representing no pain.[3,22,23] The presence and severity of the wounds was graded by calculating the Knighton wound severity score. This score is devised from clinical (eg, periwound erythema, edema), anatomic (eg, presence of exposed bone and tendon), and measured (eg, surface area, depth) wound variables.[24]

Amputation was classified as minor amputation, ie, retention of a sufficiently functional foot remnant to allow standing and walking without a prosthesis, and major amputation, as suggested by Rutherford et al.[4] The number of diagnostic procedures, ie, duplex scanning and angiography, irrespective of routine controls, was investigated. Change in health-related quality of life was assessed with the SF-36.[3,25]

Statistical analysis. Analysis was by intention of randomization. Differences between groups were compared with a *t* test, for continuous variables, and χ^2 test for categorical data. Pain, quality of life, and severity of wounds was assessed with univariate analysis of variance. The presence of wounds was assessed with the Student *t* test. Patient survival was estimated with the Kaplan-Meier method, and differences were evaluated with a log-rank test. Power analysis was performed with the bodily pain subscale of the SF36, and revealed that 90 patients must be included to refute the null hypothesis that the diagnostic accuracy between subgroups is the same (details of the calculation and assumptions are presented elsewhere[21]).

RESULTS

Ninety-six patients with 128 legs with clinically suspected CLI were randomly assigned to the conventional treatment group (62 legs of 46 patients) or the new management strategy group (66 legs of 50 patients). During the study 63 patients were excluded because of obviously severe disease. The patients included in this trial were referred to the vascular laboratory by a surgeon (62.7%), dermatologist (16.2%), internist (14.2%), or others (4.4%). Patient characteristics at baseline demonstrated no significant differences between the two groups (Tables I and II). Almost half of the patients had diabetes mellitus, hypertension, or history of coronary heart syndrome. Eighty-seven percent of legs demonstrated symptoms of rest pain, and 50% had ulcerations or gangrene.

AP, ankle-brachial index, TP, and $tcPo_2$ were high, because only patients with an uncertain diagnosis were included, with exclusion of clear cut cases (Table II). The number of diagnostic procedures and vascular interventions was not significantly different between the two management strategies (Table III). In 45% of patients a vascular intervention was performed during the total observation period. In 34 legs in the conventional strategy group and in 29 legs in the new strategy group ($P = .11$) a diagnostic procedure was performed within 1 month after inclusion.

TP was measured in 15 of 62 legs (24%) of patients assigned to the conventional strategy group. Eight of 46 patients in the conventional treatment group and 3 of 50 patients in the new treatment strategy group were lost to follow-up (not significantly different); however, occurrence of wounds or amputations in these patients was checked with the general practitioner.

Over time, pain per involved leg did not differ significantly between the two groups ($P = .9$, Fig 2, *A*). The same was true for pain in patients, as assessed with the SF-36 ($P = .07$; Fig 2, *B*), although there was a tendency in favor of the new strategy. The prevalence of wounds ($P = .04$; Fig 2, *C*) was significantly lower in the conventional treatment group, whereas severity of wounds ($P = .55$; Fig 2, D) was

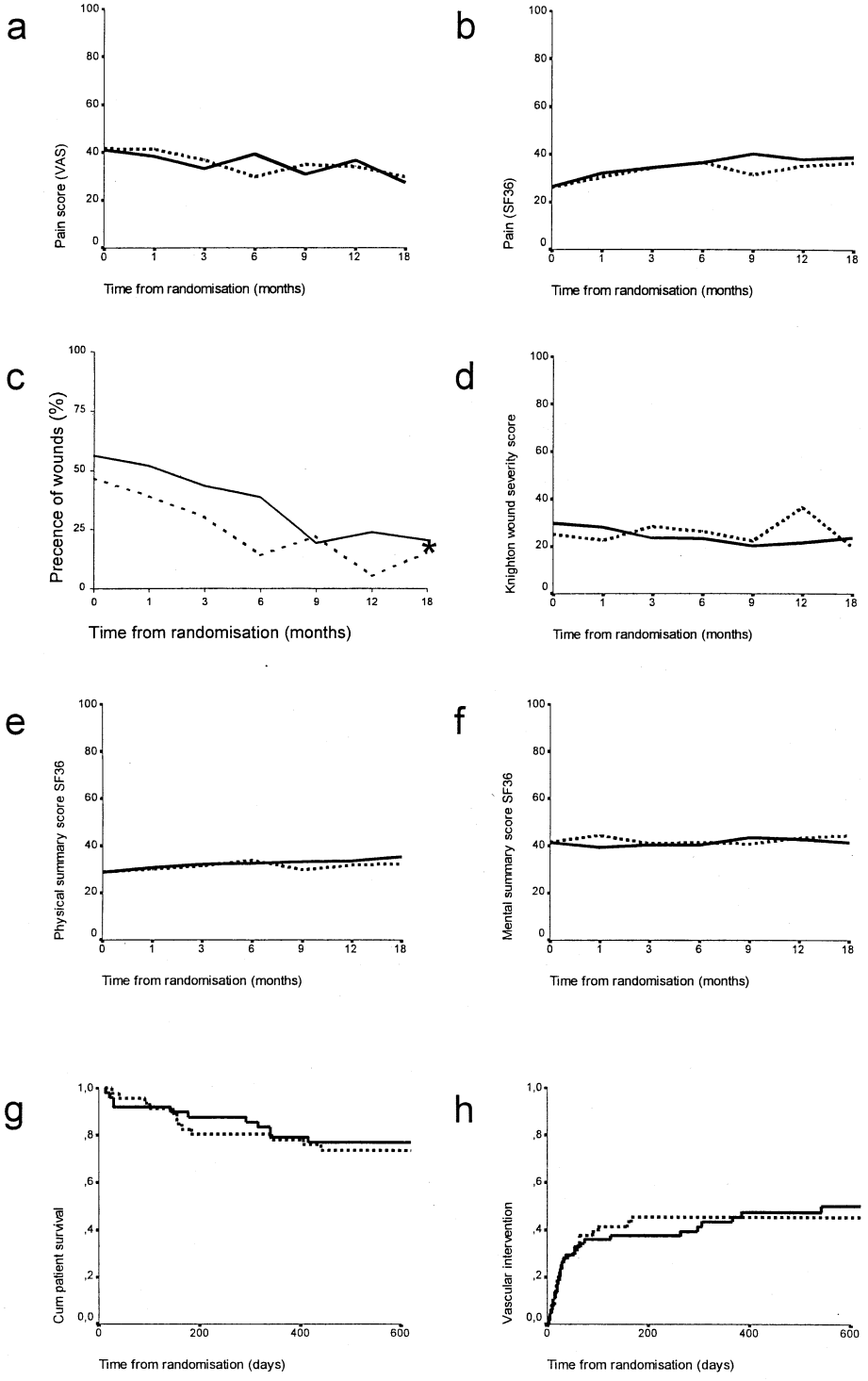

Fig 2. Graphic presentation of results of main outcome variables over time in patients in the new treatment group *(solid line)* and conventional treatment group *(dotted line)*. **A,** Pain score per leg per visual analog scale (0, no pain; 100, maximum pain). **B,** Pain score per patient according to pain score of SF-36 scale (0, maximum pain; 100, no pain). **C,** Percentage of patients with wounds. **P* = .04). **D,** Knighton wound severity score (0, minor superficial wound; 100, severe clinical wound). **E,** Physical summary score of SF-36 (0, worst clinical situation; 100, best clinical situation). **F,** Mental summary score of SF-36 (0, worst clinical situation; 100, best clinical situation. **G**, Kaplan-Meier plot of patient survival. **H,** Kaplan-Meier plot of time to first vascular intervention.

not significantly different. Quality of life assessed with the SF-36 physical and mental summary score was not significantly different between groups ($P = .10$ and $P = .28$, respectively; Fig 2, *E* and *F*).

Kaplan-Meier estimate of patient survival was not significantly different between the two groups (log-rank statistic, 0.12; $P = .7$; Fig 2, *G*). In both groups 12 patients (25%) died during the study period. The number of major and minor amputations and interventions did not differ significantly between the two groups (Table III). No patients who received conservative treatment lost a limb to amputation because of delay in intervention. Time to first intervention was not significantly different ($P = .9$; Fig 2, *F*).

DISCUSSION

Our data show that use of $tcPO_2$ and TP measurements in management of suspected CLI does not have advantage over the clinical judgment of an experienced vascular surgeon. The therapeutic choice made did not lead to a better clinical outcome in one strategy relative to the other. Furthermore, the number of diagnostic procedures was not reduced with use of these two objective measurements. Apparently the clinical eye of an experienced physician can also sufficiently appreciate the local (micro)circulation of the endangered tissues of the distal leg, as do TP and $tcPO_2$, to plan the subsequent management policy.

Many previous studies have proposed use of $tcPO_2$ and TP in diagnosis of CLI requiring intervention.[12,13,16,20,26-29] However, a true reference standard for CLI requiring vascular intervention does not exist; therefore TP or $tcPO_2$ have been compared with substitute reference standards like clinical indication for intervention,[12] wound healing,[16,20,26,30] or outcome after revascularization.[27] Therefore we chose to evaluate the value of TP and $tcPO_2$ in relation to the diagnostic process and clinical outcome in a diagnostic randomized clinical trial.[21] A randomized clinical trial is the highest standard in research. A diagnostic randomized clinical trial not only evaluates the effect on diagnosis, but also incorporates the total effect on clinical outcome, eg, side effects of tests such as angiography, and therapy, and use of the results by the physician. The lack of a true reference standard makes a diagnostic randomized clinical trial especially suitable in these cases.[21]

However, the diagnostic randomized clinical trial has some disadvantages, eg, influence of treatment on outcome, and the power and size of the trial. The expected difference in clinical outcome between randomized groups defines the size and power of the diagnostic randomized clinical trial. Many factors influence outcome, eg, effect of therapy and prevalence of the disease in the trial population. Better diagnostic information may therefore not necessarily lead to better therapeutic decisions or improvement in clinical outcome. The availability of various therapies and the capability of the physician to choose the better therapy using the diagnostic information are prerequisite for better outcome.

The present study included only patients with an uncertain diagnosis, and excluded so-called clear-cut cases, ie, patients with obviously severe or mild disease. Therefore our study truly represents the population in whom the diagnostic problem is relevant. This may also improve the power of the study, because in these patients therapeutic and clinical differences between management strategies are more likely to appear.

It can be speculated that this study might fail to show any difference because the potential value of TP is reduced by applying TP also in patients in the conventional treatment group who had incompressible arteries. However, this was considered unavoidable because withholding functional information about severity of disease in this group of patients is unethical and was unacceptable to the vascular surgeons in our department.

The present study did not show a reduction in the number of diagnostic procedures with the new strategy. The number of duplex scans with the new strategy might be falsely elevated, because in a considerable number of patients no serious obstruction that required vascular intervention could be identified at duplex scanning (n = 15). This could have been caused by our choice of a relatively high and safe cutoff value for $tcPO_2$ (35 mm Hg, rather than 30 mm Hg or even 25 mm Hg),[20] and the natural variation of the measurements, which makes it likely that in repeated measurements one of these values was below the cutoff value.[14] Measurements performed only on clinical indication might reduce the number of false low pressures considerably.

The question is whether there is still a place for use of TP and $tcPO_2$? We think that in selective cases these measurements might still be of benefit. Especially, less experienced physicians can use them as an aid to judging severity of CLI. Furthermore, TP and $tcPO_2$ measurements can offer additional information to confirm the clinical diagnosis in doubtful situations. This is particularly the case when AP is unreliable, eg, in patients with diabetes or when a leg ulcer is caused by a combination of underlying pathologic conditions. TP and $tcPO_2$ could also be used as an objective instrument in follow-up in clinical and research settings and in individual cases. However, these factors were not evaluated in the present study and need further evaluation.

We conclude that, although $tcPO_2$ and TP measurements provide additional information in selected cases, routine incorporation of these diagnostic tools does not lead to better patient outcome or reduction in the number of diagnostic or therapeutic interventions in cases in which the diagnosis of CLI is uncertain.

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Submitted Nov 14, 2002; accepted Feb 24, 2003.